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Is There a Relationship Between Asthma and Dental Caries?: A Critical Review of the Literature

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Is there a relationship between asthma and dental caries?

A critical review of the literature

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ABSTRACT

Background. The authors conducted a critical review of the literature to ascertain the strength of the scientific and professional evidence supporting an association between dental caries and the experience and severity of asthma.

Types of Studies Reviewed. In March 2010, the authors searched Medline (1976-2010) by using the Ovid Web Gateway for the terms "asthma" and ["dental caries" or "dental caries susceptibility"] appearing in studies of humans published in English. The authors eliminated conference proceedings and abstracts, opinion pieces and unpublished studies; they included case series, cross-sectional, case-control and cohort studies and clinical trials.

Results. The review yielded 27 studies described in 29 articles. The authors found that researchers have investigated the hypothesized relationship between asthma and caries by means of diverse strategies, often using asthma cases clustered in pools of patients seeking clinical care. The strongest methodological designs were more likely to reveal little support for a positive association. The authors found no strong evidence suggesting that a causal link exists. Future research incorporating better-defined covariates and longitudinal designs is needed.

Clinical Implications. Asthma per se may not be a risk factor for caries. Patients who have extreme dryness of the mouth, whose use of nebulizers is persistent, whose consumption of carbohydrates is frequent, and who have used multiple medications or have used medications over the long term necessitate cautious dental health care.

Key Words. Restorative dentistry; dental disease; asthma; dental caries; caries management; oral health; oral-systemic health associations.

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Dental and medical problems tend to coexist,[1-5] but no definitive link has been established that allows clinicians or investigators to predict one on the basis of the other. Increases in dental caries (in terms of experience, severity or both) and in asthma (in terms of severity, frequency or both) may be two parts of a larger scenario of unequal distribution of diseases or separate domains that evolve independently. This confusion is heightened further by differences in patients' access to clinical care.

In an analysis of the National Health Interview Surveys conducted from 1993 through 1996, which examined medical care, dental care, prescription drugs and vision care, researchers found that 7.3 percent of American children younger than 18 years had at least one such health care need.[3] Dental care was the most common unmet need (5.3 percent), and lack of insurance and low socioeconomic status (SES) were strong predictors of unmet health care needs overall. Infections and asthma contributed to more than one-half of all hospitalizations among children aged 1 to 4 years and nearly one-third of all hospitalizations among children aged 5 to 9 years.

Asthma affects an estimated 20 million Americans,[6] and the preva-

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lence of asthma has been increasing since the 1980s across all age, sex and racial groups. Asthma appears to be, after dental caries, the most prevalent chronic childhood disease in the United States. In the 1980s, asthma was associated with 500,000 hospitalizations and 6.5 million office visits to physicians annually.[7] Based on national survey results published in the late 2000s, 7 percent of adults and 9 percent of children in the United States have asthma, necessitating 10.6 million office visits to physicians. In 2006, 444,000 hospital discharges involved patients whose first-listed diagnosis was asthma.[8,9]

Caries remains an important health problem across all age groups in the United States, but it is documented better in children than in adults. Mixed evaluations have resulted from looking at trends in terms of considering a glass half full or half empty. Namely, dental caries prevalence for many children has decreased in the past few decades,[10-12] but although the proportion of caries-free children has increased, the reduction in caries burden has not been shared equally among children.[13(pp10,11)] If the caries experience in primary and permanent teeth is considered jointly, the proportions of caries-free children continue to decrease in adolescence: data from the Third National Health and Nutrition Examination Survey, conducted from 1999 through 2004, indicated that 59 percent of 12- to 19-year-olds have had dental caries in their permanent teeth and 23 percent have untreated decay.[14]

Our rationale for undertaking this review of the literature is that people with asthma may become more susceptible to caries directly (through biological mechanisms), indirectly (through pharmacological mechanisms) or both. The 2000 report of the U.S. surgeon general titled Oral Health in America[15] indicated that asthma and caries, together with learning difficulties and social problems, are correlated closely enough with social disadvantage to be designated sentinel diseases. Questions that remain to be addressed are whether a link exists between asthma and caries and if so, what its nature is. Is the association between increased severity and frequency of asthma conditions and increased experience of caries a direct relationship? Is this relationship pharmacological or biophysiological in nature? Are asthma and caries separate sequelae of poor access to different health care services? Or are all of these the case? We present a semistructured review of the scientific and professional literature in which we attempted to ascertain the strength of the evidence supporting an association between asthma and caries. Because many reports pertain to children, we will emphasize, but not limit the review to, younger age groups.

MATERIALS AND METHODS

We conducted a general literature review with substantial structured review components, rather than a definitive, systematic review.

Sources. In March 2010, two oral epidemiologists (G.M. and O.L.) searched Medline for articles published from 1976 through 2010 by using the Ovid Web Gateway. The search strategy included the National Library of Medicine Medical Subject Headings (MeSH) terms ("asthma" and ["dental caries" or "dental caries susceptibility"]). They limited the search to studies involving human participants and published in English. We designed this search strategy to ensure high sensitivity initially, rather than high specificity. Although we did not contact editors or authors (with one exception), we undertook a hand-search review of the list of references in every article we identified.

Study selection. Two oral epidemiologists (G.M. and J.D.S.) reviewed the list of titles and abstracts for articles generated by the search engine to identify those that appeared to be research reports addressing the structured review question. They explicitly eliminated conference proceedings and abstracts, editorials, opinion pieces and unpublished studies. Owing to the general nature of the question (association) and the limited number of research studies available,

ABBREVIATION KEY. BOP: Bleeding on probing. **dfs:** Decayed or filled surfaces (primary teeth). **DFS:** Decayed or filled surfaces (permanent teeth). **defs:** Decayed, extracted or indicated for extraction, or filled surfaces (primary teeth). **deft:** Decayed, extracted or indicated for extraction, or filled (primary) teeth. **dft:** Decayed or filled (primary) teeth. **dmfs:** Decayed, missing or filled surfaces (primary teeth). **DMFS:** Decayed, missing or filled surfaces (permanent teeth). **dmft:** Decayed, missing or filled (primary) teeth. **DMFT:** Decayed, missing or filled (permanent) teeth. **DS:** Decayed surfaces (permanent teeth). **ENO:** Exhaled nitric oxide. **FS:** Filled surfaces (permanent teeth). **MeSH:** Medical Subject Headings. **NA:** Not applicable. **NHANES III:** Third National Health and Nutrition Examination Survey. **SES:** Socioeconomic status. **SGH:** Salivary gland hypofunction. **WHO:** World Health Organization.

they included most evidence levels in the review—that is, cross-sectional, case-control and cohort studies, as well as clinical trials. Study selection criteria dictated that an article describe a clinical, epidemiologic, microbial or survey investigation of dental caries in relation to asthma-related disease presentations and that it present a clinical measurement of caries (such as decayed, missing or filled [permanent] teeth [DMFT]; decayed, extracted or indicated for extraction, or filled surfaces [defs] of primary teeth; and so on) as the outcome variable. We read the articles that appeared to qualify for inclusion.

Evaluation. We abstracted the articles, evaluated the quality of the measures used in the studies and reviewed the studies' designs and analytic methods. We also sought to identify variables that indexed socioeconomic status, social class or any social position measure; we noted participant recruitment, measures of caries and asthma, and statistical analysis approaches. We discussed and resolved differences in interpretation; our review was not masked.

For studies in which investigators had performed multiple bivariate tests and reported exact probabilities, we used Holm's sequential strategy with $\alpha = .05$ as the level of significance to reduce the familywise error rate. For example, for studies in which three tests were performed, we ranked the computed P values in increasing order, comparing the smallest value (α_{H1}) with .05/3, the next smallest significance level (α_{H2}) with .05/2 and the last (that is, the largest) (α_{H3}) P value with .05/1, or $\alpha_H = .05$. We deemed comparisons statistically significant if $P < \alpha_H$.

RESULTS

By using this search strategy, we found 31 citations, yielding 27 separate studies in 29 reports published between 1976 and March 2010 (Table 1[16-42]). We found no systematic or structured reviews regarding the specific topic of our review. The first study assessing the association between caries and asthma appeared in 1979.[16] Although many studies were carried out in Scandinavia (particularly in the more distant past), many countries are represented; North America and Asia recently have become more predominant in this area of research.

The studies we identified largely were case-control studies (Table 2, page 1072), more often than not either using patient records or recruiting patients from clinical services (dental or lung clinics becoming more common settings in recent years). Only two studies provided a longitudinal perspective,[27,31] and one involved a retrospective assessment.[21] Table 2 presents studies in terms of their negative or positive results for each dentition, as well as a hierarchy of research designs. We also included four cross-sectional studies and four case series. Researchers conducting case-control studies were almost as likely to find a positive association as they were to find no association or an ambiguous relationship (particularly across age groups or according to intensity of clinical management of asthma). But researchers conducting the largest studies (in terms of the number of participants) and the studies least likely to be affected by the use of convenience samples or the collection of cases from asthma clinics[27,28,40] found negative or inverse associations between caries experience and asthma experience. The only large-scale study that failed to follow this trend was a Danish study[31]; as with a number of studies that we noted in Tables 1 and 2 for the possible shortcoming of not using multivariable analyses in scrutiny of the role of diverse variables, the investigators in the Danish report found a positive association. The study had mixed results, and the investigators provided an uncertain description of analyses.

Researchers conducting case-control studies were almost as likely to find a positive association between asthma and caries as they were to find no association or an ambiguous relationship.

A formal meta-analysis of the results of the studies we reviewed was not feasible because of the heterogeneity of variables, measurements and statistical approaches; the frequent lack of a complete description of fixed-effects or random-effects models or a justification of whether the chosen models accounted for predictors of study results; and infrequent use of dose-response models. Few studies involved an explicitly masked design for clinical examiners.

In total, researchers investigated the hypothesized relationship between asthma and caries by using a variety of methods, most of them resorting to the study of asthma cases previously defined

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TABLE 1

Chronological description of studies addressing the association between asthma and caries, 1976–2010.

SOURCE, YEAR; COUNTRY	PARTICIPANTS	TYPE OF STUDY	INCLUSION CRITERIA
Hyyppä and Paunio,[16] 1979; Finland	30 patients with asthma (10-12 years old) and 30 control participants matched according to age, sex, living conditions and fluoride content in water	Case-control	Children with asthma
Storhaug,[17] 1985; Norway	All children aged 1 to 6 years with any of 10 disabilities (N = 433) in a referral hospital for dental care from 1976 through 1978; 47 children (11 percent) had asthma	Case series	Children with at least one disability seeking care at a referral hospital
Bjerkeborn and Colleagues,[18] 1987; Sweden	61 patients with asthma (5-18 years old) were further classified according to disease severity and medication use and were matched according to age, sex and water fluoridation with 55 control participants	Case-control	Children with asthma using various regimens of antiasthma medications
Ryberg and Colleagues,[19] 1987; Sweden	24 patients with asthma (10-20 years old) using inhaler medications with 24 matched control participants	Case-control	Children with asthma currently using β_2 adrenoceptor agonists
Ryberg and Colleagues,[20] 1991; Sweden	21 patients with asthma from the authors' 1987 study, four years later (14-24 years old), using inhaler medications; same control participants as in the 1987 study	Case-control	Children with asthma currently using β_2 adrenoceptor agonists
Arnrup and Colleagues,[21] 1993; Sweden	Hospital records for 269 inpatients (mean age ± standard deviation [SD] 7.7 ± 5.1 years), of whom 9 percent received diagnosis of asthma	Retrospective	All inpatients seen at a pediatric dental clinic within a two-year period referred from regional hospital; unclear how many participants had systemic or mental health conditions
Herrström and Högstedt,[22] 1994; Sweden	137 schoolchildren (13-15 years old) in cross-sectional survey (conducted via questionnaire and telephone) in a junior high school; review of dental records (55 percent response rate)	Cross-sectional	Schoolchildren in a midsized town who consented to participate in survey, contrasting allergic disorders and caries among children
Kankaala and Colleagues,[23] 1998; Finland	51 children with asthma, with 102 control participants matched for sex and age	Case-control	All children with asthma born in the 1980s living in three communities
Laurikainen and Kuusisto,[24] 1998; Finland	33 patients with asthma (25-50 years old) classified for severity in terms of medication regimens, with 24 control participants matched according to age and sex	Case-control	Adults with asthma who were receiving various medication regimens who were not using psychiatric medications and did not have diabetes

* DMFS: Decayed, missing or filled surfaces (permanent teeth).
† dmft: Decayed, missing or filled (primary) teeth.
‡ DFS: Decayed or filled surfaces (permanent teeth).
§ dfs: Decayed or filled surfaces (primary teeth).
¶ SES: Socioeconomic status.

ASTHMA MEASURES	CARIES MEASURES	RESULTS	ASSOCIATION
Children with "long-term extrinsic asthma"	DMFS,* salivary flow rate, buffer capacity, lactobacilli, electrolytes	Investigators found no differences between case and control participants except for lower experience of calculus (presence or absence) among children with asthma; however, the authors reported no statistical test for the difference	Negative
Medically confirmed diagnosis of asthma	dmft† (any permanent teeth present were added to the primary teeth counts); bitewing radiographs	Children with asthma seemingly had more carious teeth than did other chronically ill preschool children, but reporting of results is unclear; children in study had higher dmft than comparable Norwegian children, but authors reported no statistical test	Ambiguous
Children were treated at a university hospital for asthma but did not have other systemic diseases	Stimulated saliva specimens, buffer capacity, lactobacilli, dental plaque, gingival index, incipient and cavitated caries, bitewing radiographs, dietary and fluoride variables	Only saliva secretory rate in the younger children with severe asthma was lower than that in the control participants; no other variable was different; the authors did not conduct multivariable analysis, so statistical adjustment for covariates could not be made	Negative
Children receiving β_2 agonists for asthma	Stimulated saliva specimens and secretion of parotid saliva, dental plaque, incipient and cavitated caries, bitewing radiographs, dietary data; examiner was masked as to asthma status	Only saliva secretory rate, total protein and amylase were lower in children with asthma; DFS‡ and other components' scores were not significantly different between case and control participants	Mainly negative
Teenagers and young adults receiving β_2 agonists for asthma	Stimulated saliva and parotid saliva, buffer capacity, lactobacilli and *Streptococcus mutans*, dental plaque, incipient and cavitated caries, bitewing radiographs, dietary data; examiner was masked as to asthma status	Saliva secretory rate, parotid saliva and saliva total protein, individual protein constituents and electrolytes were reduced in cases; case participants had higher titers for lactobacilli; incipient or cavitated caries and incident caries were higher among case participants; researchers made no adjustments for multiple comparisons	Positive
Medically confirmed diagnosis of asthma	Gingival/periodontal, soft-tissue and occlusal abnormalities; dental caries (primary and permanent teeth)	Children with asthma had significantly more dfs§ than did other inpatient children; no information provided about permanent teeth; researchers did not conduct a multivariable analysis	Mainly positive
Bronchial reversibility test, questionnaire data and use of medications and medical care for childhood asthma, eczema, allergic rhinoconjunctivitis in prior 12 months	Prevalence of tooth surfaces restored with amalgam in publicly available school dental health examination; no untreated carious lesions were found	No association with increased or decreased likelihood of amalgam restorations discernible across the various definitions of allergic disorders in children; children with higher SES¶ were marginally more likely to report asthma symptoms and those with lower SES were more likely to have received amalgam restorations; authors should have conducted multivariable analyses to adjust for covariates	Negative
Children receiving asthma medications, inhaled corticosteroids and β_2 agonists, according to regional data sets	Authors obtained from dental records data regarding timing of placement of first restorations in, and extractions (for caries) of, primary and permanent teeth	Children with asthma generally received restorations on upper primary molars (relative risk, 2.5), and perhaps other teeth, earlier than did control participants, but the report is limited to graphical display of survival curves; authors indicated that tooth extractions were higher among children with asthma but did not provide data	Mainly positive
Adult patients treated at a lung clinic in a teaching hospital	Stimulated saliva specimens and saliva pH, dental plaque, calculus, periodontal and gingival indexes, dietary data for sugar intake, education and occupation, tobacco and alcohol intake, oral hygiene	Participants with asthma had a lower SES than that of control participants; only salivary secretory rate was significantly higher and periodontal status was better in control participants; DMFT was not significantly different between case and control participants	Mainly negative

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TABLE 1 (CONTINUED)

SOURCE, YEAR; COUNTRY	PARTICIPANTS	TYPE OF STUDY	INCLUSION CRITERIA
McDerra and Colleagues,[25] 1998; Great Britain	100 children with asthma (4-16 years old) matched according to age, sex, race and SES with 100 control participants; children were divided into two age groups, 4 to 10 years and 11 to 16 years	Case-control	Children with asthma using an inhaler
Milano,[26] 1999; United States	179 children with asthma aged 2 to 13 years; 165 siblings without asthma served as control participants; data based on review of 1,500 dental records	Case-control retrospective record view	Participants were selected on the basis of having asthma and taking medication, "not having early childhood caries" and having a sibling who did not have asthma
Meldrum and Colleagues,[27] 2001; New Zealand	As part of a large national cohort study, authors recruited 1,037 children at age 3 years and assessed them every two years until they reached the age of 18 years; 867 underwent dental examinations at age 18 years	Cohort	Children with asthma using medication or not, derived from a national study of health, development and well-being in a cohort evaluated across time
Shulman and Colleagues,[28] 2001; United States	6,938 children aged 4 to 16 years; data collected via national survey	Case-control	Randomly selected participants enrolled in the Third National Health and Nutrition Examination Survey
Reddy and Colleagues,[29] 2003; India	250 children 3 through 18 years old divided according to primary, mixed and permanent dentitions; also divided on the basis of asthma severity and type of medication	Cross-sectional	All children with bronchial asthma seeking care at various hospitals
Eloot and Colleagues,[30] 2004; Belgium	140 children with asthma (3-17 years old), divided into groups according to time and severity of asthmatic symptoms and medication use	Case series	Children with asthma using an inhaler with varying degrees of use according to severity
Wogelius and Colleagues,[31] 2004; Denmark	4,920 children in a birth cohort yielded 1,496 (30.4 percent) aged 3 to 5 years and 926 (18.8 percent) aged 5 to 7 years who had received one or more asthma medications	Cohort	All children born in a large geographical area in 1993 who still lived there in 2000 and who received medication to treat asthma
Bimstein and Colleagues,[32] 2006; United States	300 dental records selected from dental school records, leading to 291 "clearly recorded" medical status records (mean age ± SD, 7.1 ± 3.4 years)	Case series	291 children seen at a pediatric dental clinic whose records were "randomly" selected: 43 percent had no systemic conditions, 17 percent had asthma, 40 percent had other systemic or mental conditions

DMFT: Decayed, missing or filled (permanent) teeth.
** dmfs: Decayed, missing or filled surfaces (primary).
†† DS: Decayed surfaces (permanent teeth).
‡‡ FS: Filled surfaces (permanent teeth).
§§ dft: Decayed or filled (primary) teeth.
¶¶ deft: Decayed, extracted or indicated for extraction, or filled (primary) teeth.

ASTHMA MEASURES	CARIES MEASURES	RESULTS	ASSOCIATION
Children diagnosed as having asthma and using an inhaler	DMFT,[#] DMFS, dmft, dmfs** and plaque scores used for caries diagnosis	Children with asthma had higher DMFT and DMFS scores than did control participants, but only the children aged 4 through 10 years had higher plaque scores; primary teeth scores were not significantly different	Mainly positive
Medically confirmed diagnosis of asthma, using some asthma medication	dmft, dmfs, DMFT, DMFS	dmfs and DMFS were higher in children with asthma than in children in control group; use of statistical tests unclear	Ambiguous
Children with long-term asthma ("wheeze determined" and "medication determined") identified at ages 9, 11, 13 and 15 years	Three-year net increments of DS,[††] FS[‡‡] and DFS	There was no significant caries increment difference between children with and without asthma; authors should have conducted multivariable analyses to adjust for covariates	Negative
Children with physician-diagnosed asthma, as reported by parents, at all severity levels; various medications used	DMFS due to disease, excluding tooth loss caused by trauma or orthodontics, and overall DMFS; for primary dentition, dfs and dft[§§]	Children with asthma aged 4 to 10 years at all severity levels had scores similar to those of the control participants, but children with severe asthma had DMFS scores significantly lower than those of the control participants; similarly, children with severe asthma 11 through 16 years old had DMFT scores significantly lower than those of control participants	Negative
Children classified as having physician-diagnosed mild, moderate or severe asthma, according to four medication groups: inhaler, syrup, tablet and combination	deft[¶¶], DMFT	Caries prevalence increased with asthma severity; highest caries prevalence seen in those taking syrup medication, which authors explained as being because of the cariogenic carrier; authors should have conducted multivariable analyses to adjust for covariates such as SES and age	Positive
Children diagnosed as having asthma who were using an inhaler and undergoing a routine examination at a teaching hospital	DMFT, DMFS, dmft, dmfs, plaque scores, gingival bleeding, dental attitudes, dental awareness and oral hygiene, dietary and fluoride habits; examiner was masked as to asthma status	Children with asthma had largely reasonable oral hygiene and dietary habits; authors found no dose-response relationship between asthma severity or duration and caries	Negative
Children receiving asthma medications, inhaled corticosteroids and β_2 agonists, according to data from regional data sets	Caries in primary canines and molars and in any permanent teeth	No increased caries experience in primary teeth, but the relative risk of caries in permanent teeth of children receiving two medications was 1.62 (95 percent confidence interval [CI]: 1.03-2.65) only among children aged 3 to 7 years; the multiple tests and unclear interpretation of 95 percent CI is a cause for concern; authors should have conducted multivariable analyses to adjust for covariates	Mainly positive
Parents confirmed asthma diagnosis; children were receiving asthma treatment	dmfs, DMFS, plaque and calculus indexes, bleeding on probing (BOP), parental report of disorders, "presence of tooth discoloration"	Children with asthma and (to a lesser extent) children with other conditions had higher experience of toothache, higher dmfs and DMFS (no distinction between components was offered) and higher experience of calculus, plaque and BOP; authors should have conducted multivariable analyses to adjust for covariates	Positive

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TABLE 1 (CONTINUED)

SOURCE, YEAR; COUNTRY	PARTICIPANTS	TYPE OF STUDY	INCLUSION CRITERIA
Ersin and Colleagues,[33] 2006; Turkey	106 children with asthma (6-19 years old) and 100 healthy control participants matched for age and SES, divided into two groups, 6 to 10 and 11 to 19 years old	Case-control	Children with asthma using asthma medication who had not received antibiotics in preceding three months
Milano and Colleagues,[34] 2006; United States	Parents of 156 children with asthma from authors' 1999 study, investigating (via survey) length of use of, dosage of and combinations of medications	Case series	All children with asthma who had participated in the authors' 1999 study
Wierchola and Colleagues,[35] 2006; Poland	326 children with asthma (3-15 years old) in a pediatric hospital and 326 control participants from local schools, matched for age; children were divided into age groups	Case-control	Children with asthma using medication (β-adrenergic agonists or glucocorticoids) but not having any other chronic condition
Khalilzadeh and Colleagues,[36] 2007; Iran	45 children with asthma (mean age ± SD, 11 ± 3 years) who were outpatients in a lung clinic, compared with 46 control participants (no details about matching provided) (mean age ± SD, 11 ± 0.6 years); investigation of combinations of medications	Case-control	Children with asthma using medication (β-adrenergic agonists or glucocorticoids)
Shashikiran and Colleagues,[37] 2007; India	Among 143 patients initially chosen, authors examined 105 children with asthma (6-14 years old) and matched them (criteria unclear) with 106 control participants	Case-control	Children with asthma
Mazzoleni and Colleagues,[38] 2008; Italy	30 patients with asthma (mean age ± SD, 9 ± 2 years) seeking care at a teaching hospital lung clinic classified according to disease severity and compared with unmatched control participants of about same age who sought care at dental school for regular checkups	Case-control	Children with asthma using short-acting β agonists with a corticosteroid for at least six months
Stensson and Colleagues,[39] 2008; Sweden	127 children with asthma (3 and 6 years old) matched with 117 control participants according to age and sex	Case-control	3-year-old and 6-year-old children with asthma with or without long-term use of medications—usually associated with more severe disease—and frequent or infrequent use of medications
Tanaka and Colleagues,[40] 2008; Japan	21,792 schoolchildren (6-15 years old) in cross-sectional survey of all elementary and junior high schools, adjusted for SES, sex, age, siblings, smoking and paternal allergies	Cross-sectional	Schoolchildren in a large geographical area, contrasting allergic disorders among children and parents and caries among children

ASTHMA MEASURES	CARIES MEASURES	RESULTS	ASSOCIATION
Patients with asthma seeking pediatric care who had used medications for at least one year	DMFS, DMFT, dmfs, dmft, salivary flow rate, buffer capacity, saliva protein and electrolyte composition, *S. mutans* counts, three-day diet diary and oral hygiene patterns; examiner was masked as to asthma status	Only children in the group aged 6 to 10 years had significantly increased dfs and DMFS scores when compared with their matched control participants; lower pH and salivary flow rates were present among children with asthma in the two age groups (6-10 years and 11-19 years)	Positive for children aged 6 to 10 years
Medically confirmed diagnosis of asthma; use of some asthma medication	DMFT and DMFS for permanent dentition; dft and dfs for primary dentition	Children who took asthma medications more frequently were 2.5 (primary dentition) and 3.5 (mixed dentition) times as likely to experience caries, but children who had received medication for two or more years were less likely to have caries	Mainly positive
Patients with asthma seeking care at a referral service for pediatric care and using specified medications for an undetermined length of time	DMFT and dmft	Multiple comparisons across indexes for each year of age (a total of 72 *t* tests) offered relatively few significant differences (seven across both dentitions), all of them suggesting that case participants had scores higher than those of control participants	Negative until adolescence
Medically confirmed diagnosis of asthma; use of some asthma medication	DMFT; lactobacilli and *S. mutans* counts	Lactobacilli counts across case and control participants were not different, but *S. mutans* counts were; case participants had DMFT scores (mean ± SD, 4.3 ± 2.8) higher than those of control participants (3.9 ± 2.5); children receiving β_2 agonists had higher DMFT scores than those of control participants, but not of those who were treated with corticosteroids and β_2 agonists (DMFT scores not supplied); although authors cited multivariable analyses in the abstract, it is unclear what those findings were or for which variables they made adjustments	Positive
Children receiving asthma medications divided into three groups according to medication type: beclomethasone inhaler, salbutamol (albuterol) inhaler and salbutamol tablets	DMFT, DMFS, dft, dfs	Children using salbutamol inhalers had the largest caries experience, but the study design (which included a one-year follow-up) and analysis were unclear	Positive
Children who were treated at a university hospital for asthma with a specified medication regimen, but who did not have other systemic diseases	Stimulated saliva specimens, buffer capacity, lactobacilli and *S. mutans*, dental plaque, DMFT and dmft, dietary and fluoride variables (nonfluoridated water supplies); examiner was masked as to asthma status	DMFT was higher among case participants compared with control participants, but dmft was not; bacterial counts were higher and buffer capacity was lower in children with asthma; authors should have conducted multivariable analyses	Positive
Patients with asthma seeking pediatric care whose diagnosis was confirmed by parents and whose disease ranged from mild to very severe	dfs (and radiographs) as well as incipient lesions; visible plaque, lactobacilli and *S. mutans* cultures, buffer capacity; survey for dietary patterns, mouth breathing, oral hygiene	Only the rate of dfs (cavitated lesions) in the 3-year-old group was higher among children with asthma (separately related to increased consumption of sugary drinks, visible plaque, mouth breathing and likelihood of having immigrant status)	Mainly negative
Parental response to questionnaires (75 percent response rate) regarding child's, mother's or father's wheezing, asthma, atopic eczema, allergic rhinoconjunctivitis in preceding 12 months	At least one decayed or filled tooth (unclear if primary teeth were included) in mandatory annual school oral health examination	No association with increased or decreased likelihood of allergic disorders in child or parents in children with no decayed or filled teeth, and children with at least one affected tooth; only exception was children with allergic rhinoconjunctivitis, who were less likely to have caries if their parents had a positive history of allergy	Negative or inverse

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TABLE 1 (CONTINUED)

SOURCE, YEAR; COUNTRY	PARTICIPANTS	TYPE OF STUDY	INCLUSION CRITERIA
Anjomshoaa and Colleagues,[41] 2009; United States	Authors analyzed dental records data for 318 patients (mean age, 41.7 years; range, 17-84 years) adjusting them for medications, sex, age, infections, smoking status and ethnicity	Cross-sectional data mining of dental records	Patients seeking care at a dental school who had agreed to have their dental and medical histories used for research in a DNA repository and who had reported asthma alone or with three other conditions
Mehta and Colleagues,[42] 2009; India	80 children with asthma and adults (mean age ± SD, 17.4 ± 4.3 years) matched with 80 control participants according to age, SES and sex	Case-control	Patients with bronchial asthma seeking treatment at chest medicine outpatient service who had used β agonists or corticosteroids for at least six months; control group was composed of people who did not have asthma, matched according to age, sex and SES

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and clustered in pools of patients seeking asthma or dental care. Whereas we found 13 positive, 13 negative and two ambiguous associations in the studies—and whereas the investigators in the two studies reported in separate articles changed the orientation of their findings[19,20,26,34]—the strongest methodological designs were more likely to establish little support for a positive association between asthma and caries.

DISCUSSION

Five actual or hypothesized links give credence to the asthma-caries association:

- epidemiologic evidence, whereby people with asthma have higher or lower caries experience;
- pathological changes in the immunological and electrolyte properties of saliva in people with asthma;
- physiological changes in the amount or composition of saliva when airway disorders occur (as in chronic mouth breathing);
- established salivary gland hypofunction (SGH) effects of medications used to treat asthma or related conditions;
- inclusion of cariogenic sweeteners (such as fructose) as carriers in inhaler medications, commonly used for the long term.

Epidemiologic evidence regarding caries. Several investigators have found that people with asthma are at higher risk of experiencing dental caries than are those who do not have asthma. Other investigators have not found such an association. Table 1 presents a summary of studies evaluating asthma and caries experiences. Table 2 outlines the overall balance of evidence, slightly suggesting a lack of positive association between asthma and caries.

Changes in saliva: physiological-pharmacological and quantitative-qualitative reports. Although epidemiologic evidence supporting the asthma-caries association is equivocal, saliva plausibly plays a key role in the biological or pharmacological interactions between the two conditions. Saliva performs multiple roles in maintaining oral health.[43] Several specific macromolecules bind and inactivate cariogenic bacteria. This, along with the buffering capacity of saliva, helps protect enamel from the destructive action of these organisms. Statherins and proline-rich proteins promote mineralization of enamel by keeping the saliva supersaturated with calcium phosphate salts. In addition, the salivary glands secrete fluoride ions into the oral cavity. Several research groups have investigated changes in saliva in participants who had asthma compared with those in participants who did not have asthma, as well as with those in participants who had other diseases.[44] More recently, Hyyppä[45] found that phosphorus, but not calcium, in whole and parotid saliva was elevated in participants with asthma compared with that in age- and sex-matched control participants. Immunoglobulin E, along with histamine and lysozyme, in whole saliva from people with asthma was higher than that in matched control partici-

ASTHMA MEASURES	CARIES MEASURES	RESULTS	ASSOCIATION
Authors incorporated data for dental-school patients into a data-only study retrospectively; patients self-reported medical history of asthma, three other systemic conditions and various covariates	DMFS and DMFT, further categorized above and below the means (50 and 15)	Just as in patients with epilepsy, patients with asthma were found to be more prone to higher DMFT scores than were people without asthma, with an interaction for female sex (DFMT of 15.3 versus males' DMFT of 15.4); many more variables tested were not significant	Positive
Patients with bronchial asthma (categorized as moderate and severe) who had used β agonists or corticosteroids for at least six months	DMFS and DMFT	DMFT and DMFS higher among patients with asthma (mean scores ± SD, 3.7 ± 2.0 and 6.4 ± 4.6, respectively) than among control participants (mean scores ± SD, 1.3 ± 1.0; 2.1 ± 2.2, respectively); trends more marked among people with moderate, as opposed to severe, asthma; age, sex and type of medication were not significant; duration of asthma and DMFT/DMFS scores were correlated significantly	Positive

pants. The results of these studies suggested that the complex inflammatory conditions known collectively as asthma may alter salivary composition. However, the investigators conducting these studies did not control for the extrinsic source of variation contributed by asthma drugs.

Many drugs reduce salivary function significantly, and some of this attenuation is predictable on the basis of the drug's mechanism of action. The drugs most often associated with SGH are those that interfere with autonomic control of the gland or with ion and water movement. These include drugs with anticholinergic actions, centrally acting antihypertensive agents and diuretics. Importantly, the SGH effect may increase with the number of drugs taken, but there is no empirically based taxonomy of the potential for SGH under polypharmacy conditions. A dual cross-sectional assessment of older adults showed that use of asthma drugs was associated with an increase in coronal caries of almost a double increment in five years.[46] Asthma drugs have administration modalities that promote caries through other mechanisms, beyond the active ingredients of inhalers' having an SGH effect. Inhalers have a relatively low pH (5.5), contain cariogenic sweeteners as carriers or both.[27] Patients commonly use inhalers for the long term and at frequent intervals, and people often misuse them by placing the medication in the mouth rather than in the upper airways, thus enhancing the cariogenic insult.

Ryberg and colleagues[19,20] attempted a longitudinal evaluation of children with asthma. They found that children with asthma who were exposed to daily inhalation of a β_2-selective adrenergic bronchodilator (such as terbutaline or albuterol) exhibited a decreased salivary flow rate (whole and parotid) and diminished protein output when compared with age-, sex- and SES-matched control participants. Although salivary function in the participants with asthma was attenuated after they had received the drug for at least one year, the DMFT scores of the two groups did not differ significantly. When these same children had received the drug for more than five years, the participants with asthma exhibited a significantly higher incidence of caries.[20] On the other hand, Bjerkeborn and colleagues[18] found that caries prevalence in patients with severe asthma (those having more than 10 attacks per year) who had received long-term medication was not significantly different from that of patients with moderate asthma who were not receiving long-term medication therapy. Kargul and colleagues[47] compared pH levels within interdental spaces in participants after they used inhaler drugs, chewed gum or drank water, and they suggested that β_2 agonists and corticosteroids could be causing substantial declines in oral pH levels.

Another mechanism possibly involved is mouth breathing, commonly associated with airway disorders. Although the inverse relationship between prolonged mouth breathing and decreased salivary levels is both intuitive and supported by

TABLE 2

Studies according to strength and type of research design, adequacy of statistical tests to establish the asthma-caries relationship, and confirmation of relationship separately for the two dentitions.*

AUTHOR	DESIGN	DATA ANALYSIS ADEQUATE	RELATIONSHIP BETWEEN DENTITION AND ASTHMA	
			Primary Dentition	Permanent Dentition
Meldrum and Colleagues[27]	Cohort	No†	Yes	No
Wogelius and Colleagues[31]	Cohort	No†	No	Yes
Arnrup and Colleagues[21]	Retrospective	No†	Yes	Not applicable (NA)
Milano[26] (1999)	Case-control	Yes‡	Yes	Yes
Wierchola and Colleagues[35]	Case-control	No§	Yes	Yes
Kankaala and Colleagues[23]	Case-control	Yes¶	Yes	No
Khalilzadeh and Colleagues[36]	Case-control	No†§	NA	Yes#
Ersin and Colleagues[33]	Case-control	No§	NA	Yes*
Shashikiran and Colleagues[37]	Case-control	No†	Yes	NA
Bjerkeborn and Colleagues[18]	Case-control	No†	No	No
Stensson and Colleagues[39]	Case-control	Yes	Yes	NA
Mazzoleni and Colleagues[38]	Case-control	No†	No	Yes
McDerra and Colleagues[25]	Case-control	Yes	No	Yes
Mehta and Colleagues[42]	Case-control	Yes	NA	Yes
Ryberg and Colleagues[20] (1991)	Case-control	No§	NA	Yes**
Hyyppä and Paunio[16]	Case-control	Yes	No	No
Laurikainen and Kuusisto[24]	Case-control	Yes	NA	No
Ryberg and Colleagues[19] (1987)	Case-control	No†§	NA	No**
Shulman and Colleagues[28]	Case-control	Yes	No	No
Anjomshoaa and Colleagues[41]	Cross-sectional	Yes	NA	Yes
Herrström and Högstedt[22]	Cross-sectional	No†	NA	No
Reddy and Colleagues[29]	Cross-sectional	No†	Yes	Yes
Tanaka and Colleagues[40]	Cross-sectional	Yes†† ‡‡	No	No
Bimstein and Colleagues[32]	Case series	No†	Yes	Yes
Eloot and Colleagues[30]	Case series	Yes	No	No
Milano and Colleagues[34] (2006)	Case series	Yes‡	Yes	Yes
Storhaug[17]	Case series	No¶	No	No

* "Yes" means the relationship was confirmed, "No" means the relationship could not be confirmed and "Not applicable" (NA) means the relationship was not addressed for either dentition.
† Multivariable analysis not used to adjust for covariates.
‡ Participants were patients at U.S. dental schools who likely were of lower socioeconomic status than the general population.
§ Multiple tests without adjusting α.
¶ Limited reporting of results of statistical tests.
# Not statistically significant after post hoc adjustment for multiple comparisons using Holm's sequential strategy.
** Exact probabilities not provided, thus precluding adjustment for multiple comparisons.
†† Binary classification of caries may have reduced study's power.
‡‡ No distinction between primary and permanent dentition.

clinical findings of dry, swollen gingivae in mouth breathers, these phenomena have received surprisingly scant attention. Most investigators exploring the asthma-caries relationship have ignored this factor. Classification of people as mouth breathers has been addressed only in reports that lack solid validation,[48] perhaps because such clinical scores would need to be validated against objective yet cumbersome measures involving plethysmography.[49]

Hypothesized role of nitric oxide. Exhaled nitric oxide (ENO) is measured by means of a noninvasive test relying on well-established evidence that ENO increases in the presence of inflammatory airway disorders,[50] thus providing a strong diagnostic gauge.[51] Of interest to dental science is the fact that nitric oxide becomes nitric acid—a strong acid—when in contact with water.[52] Given the abundance of water in the mouth and upper airways (a patient's SGH and mouth-breathing statuses notwithstanding), its presence in combination with ENO may lead to a demineralization challenge specific to people with asthma. Direct evidence remains to be established showing that this hypothesized mechanism is consistent and of clinical effect (in erosion, caries or both).

Behavioral factors. Investigation of behavioral aspects typical of people

with asthma and relevant to oral health is missing from the published literature, by and large. Although one intuitively might expect that people with asthma would have little opportunity to add periodic professional dental care and conscientious home care to their daily lives, asthma status does not seem to be a factor that inexorably leads to worse caries outcomes. In fact, Shulman and colleagues,[28] using U.S. survey data that they adjusted for the effect of covariates, found that having asthma was associated with lower caries prevalence. Researchers found a less evident but still similar trend in a large regional study in Japan.[40] If the upswing in global asthma-rate trends indeed is related to more hygienic living conditions that help people avoid exposure to microorganisms, such environments also may explain, in part, the lack of cariogenic bacteria. Wogelius and colleagues'[31] differential findings for the primary and permanent dentitions may lend credence to this speculation (they found that primary teeth were not affected by increased caries experience among participants with asthma, but that permanent teeth were).

Study populations and age. The information in Table 2 does not make it clear whether the hypothesized asthma-caries relationship is more apparent in primary dentitions or in permanent dentitions. Although many of the articles we reviewed focused on children, the evolution of the disease and the medication regimens may modulate their effects on the dental health of a person with asthma throughout life. It is generally accepted that a definitive diagnosis of asthma is difficult to reach before a child's fifth birthday; this situation may have led to the exclusion of toddlers from participating in studies. Conversely, children with more severe asthma could be more likely to seek care and thus become study participants—because being older would have facilitated the confirmation of an asthma diagnosis. Older children would be more likely to have more numerous erupted permanent teeth. The heterogeneity of treatment intensities for asthma across age groups suggests that much more detailed characterization of such profiles is needed before researchers safely can appraise the influence of older age, asthma severity, medication use and comorbidities on caries profiles.

CONCLUSION

Considering the large number of contributing factors that may be operating in the asthma-caries relationship, it is hardly surprising that this relationship has been difficult for dental clinicians to interpret. The specific intensity of medication regimens may change, and these regimens may be modified in response to an evolving clinical scenario—leading, in turn, to physiological variation in the oral environment. The severity of asthma symptoms also varies across time. In addition, the environmental insults posed by household and outdoor allergens modulate asthma symptoms and treatment. The necessary combination of factors leading to increased caries lesions that are detectable clinically and that are present for a sufficient amount of time may be achieved only when prolonged demineralization of dental tissues offsets professional and public interventions, oral home care practices and the natural environment. On the basis of the literature, it would appear that there is no strong evidence suggesting that a causal link exists between caries and asthma. Further population-based research, incorporating better defined covariates and longitudinal designs, is needed to characterize such a link fully. ■

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